

REMARKS

I. Support for the Amendments

Claims 1-32 were originally in the application. Claims 1-25 and 38 have been canceled, and claims 29-32 have been withdrawn. Claims 26-27, 33-37, and 39-48 were previously in the application.

Claims 26-27, 33-37, and 39-50 are currently in the application. Claim 26 has been amended, and new claims 49-50 have been added.

Support for amended claim 26 and for new claims 49-50 can be found in the original specification, figures, and claims. Support for these amendments can also be found in the previous versions of these claims. No new matter has been added by virtue of these amendments.

Additional support for amended claim 26 and for new claims 49-50 can be found, e.g., from page 1, line 19, to page 2, line 6; from page 2, line 11, to page 3, lines 3-9 and 24-28; from page 6, line 13, to page 10, line 2; and in the Examples and Figures.

II. Status of the Claims

Claims 1-32 were originally in the application. Claims 1-25 have been cancelled. Claims 26-32, which were previously non-elected claims in U.S.S.N. 09/354,664, were previously in the application. Claims 26-32 were subject to a restriction requirement. Claims 26-28 were elected.

In the previous amendment, claims 26-27, 33-37, 39, 43, and 45 were amended.

Claims 26-27, 33-37, and 39-50 are currently in the application. Claim 26 has been amended, and new claims 49-50 have been added.

III. Reiteration of the Request for a Corrected Filing Receipt

On 14 November 2003, Applicants filed a Request for Corrected Filing Receipt, but did not receive it. Most recently, Applicants reiterated their request in the Response filed on 6 October 2009. Applicants continue to await a revised, corrected filing receipt, as noted in the reminder requests in the Amendments filed on 28 November 2006, 13 July 2007 (copy also provided with Request for Continued Examination on 12 October 2007), 9 May 2008, March 23, 2009, July 7, 2009, and 6 October 2009.

Applicants hereby reiterate their request to receive the Corrected Filing Receipt forthwith.

IV. The Rejection of Claims 26-27, 33-37, and 39-48 under 35 U.S.C. §103(a) is Traversed

The Examiner has maintained the rejection of claims 26-27, 33-37, and 39-48 under 35 U.S.C. § 103(a), alleging obviousness over Rogers et al. (Analyt. Biochem. 247: 223-227 [May 1997]; "Rogers & Burgoyne" or "Rogers") in view of Burgoyne (U.S. Patent 5,496,562) and in view of Kahn et al. (Methods Enzymol. 68: 268-280 [1979]; "Kahn"). Applicants respectfully traverse this rejection.

Applicants have already discussed these references at length. For the reasons already of record, as well as for the reasons below, Applicants respectfully traverse this rejection.

Previously, Dr. Walter King and Applicants' undersigned representative had been granted a telephonic interview by the Examiner on August 5, 2009. During the interview, the teachings

of Rogers and Burgoyne were discussed with respect to the outstanding rejection under 35 U.S.C. 103(a) over Rogers, Burgoyne, and Kahn.

In accordance with the Examiner's request, Applicants had submitted a Supplemental Declaration of Dr. Walter King Pursuant to 37 C.F.R. 1.132 ("First Supplemental Declaration") with the Response filed on 6 October 2009. (Although the previous Supplemental Declaration was merely entitle "Supplemental Declaration of Dr. Walter King Pursuant to 37 CFR 1.132," Applicants will refer to it as the "First Supplemental Declaration" in this document for the sake of clarity and in order to avoid confusion with the "Second Supplemental Declaration of Dr. Walter King Pursuant to 37 CFR 1.132" filed herewith.)

As noted by Dr. King in the First Supplemental Declaration, plasmid vectors are small, circular molecules of double-stranded DNA:

....The number of copies of a particular plasmid in a cell varies from one plasmid to the next depending on the mechanism by which replication is regulated. Low copy-number plasmids are present in 1-2 copies per cell. The bacterial genome of *E. coli*, which is the most common host for plasmid vectors containing recombinant DNA segments, is approximately 4.6 million base pairs, while their corresponding plasmids, such as the ColE1 family, are about 3 orders of magnitude smaller.

....This discrepancy in mass poses a significant technical challenge in the development of a suitable matrix for the efficient recovery of plasmid DNA where the binding capacity per unit area is limited. Because one of skill in the art was dealing with a poorly understood mechanism of macromolecular binding in a dried spot, the binding capacity of such treated matrices in complex media, like bacterial cultures, is not limited to just DNA, but also proteins and other macromolecules present in the culture, which further limits the number of "available sites" on the matrix. [First Supplemental Declaration, pars. 7-8.]

In the First Supplemental Declaration, Dr. King had noted the difference between the present invention and the recovery of previously purified plasmid in Burgoyne, namely, that the input DNA of the previously purified plasmid of Burgoyne was uniformly plasmid DNA "devoid of other macromolecules present in the original bacterial culture, whereas the present invention deals with unpurified samples including a large number of many types of macromolecules having a discrepancy of mass."

To illustrate how this mass discrepancy becomes problematic for the recovery of non-purified plasmids in a bacterial culture, Dr. King had provided the following hypothetical example:

If 0.1 microgram of purified pUC19 plasmid DNA (the plasmid example used by Burgoyne) was applied to FTA[®] medium, this would correspond to approximately 3.4×10^{10} molecules on the paper. If 99% (Burgoyne termed “approximately 100%”) of the DNA were detected, then approximately 1% or 3.4×10^8 molecules of plasmid DNA might not be detected. Conversely 0.1 microgram of *E. coli* DNA from a culture containing a low copy plasmid only corresponds to approximately 2×10^7 molecules of genomic *E. coli* DNA and the same number of plasmid DNA molecules, which is more than an order of magnitude lower in target molecules than the purified plasmid scenario. In the context of finite binding capacity of any substrate where the mass of DNA is independent of genome size, the 1.9×10^7 molecules of plasmid DNA which co-purified with the genomic DNA would be below the total number of plasmid DNA inputted on the paper. [First Supplemental Declaration, par. 9; all emphasis in original.]

In essence, in the First Supplemental Declaration, Dr. King was using the above as a hypothetical example as to why Burgoyne, in which purified plasmid DNA (as opposed to a sample of intact cells) was applied to FTA[®] medium, would not have rendered the present invention obvious, either alone or in combination with Rogers & Burgoyne and/or Kahn.

In the present Office Action, mailed on 26 January 2010, the Patent Office states:

As understood by the examiner, Applicant is attempting to rebut the instant case of obviousness by asserting that a person of ordinary skill in the art would not have had a reasonable expectation that plasmid DNA could have been isolated from the claimed solid support while in the presence of the host genome and other associated cellular material, due to the limited number of available sites on the support, i.e. one would not have expected that the very limited number of plasmids could bind to the solid support in the presence of the vast bacterial genomic and cellular protein material... This argument is not persuasive because: 1) Applicant has based the argument solely in the context of low copy plasmids.... Such an argument is not fully commensurate in scope with the claimed invention, which encompasses all plasmids... as well as host vectors.... and 2) with specific regard to claims 26, 27, 33-37, and 39-41, the claimed invention does not expressly require that the plasmid DNA actually come in contact with the solid

support....[Office Action, p. 5; underline in original, other emphasis added; citations omitted.]

With respect to the second point, Applicants have amended independent claim 26 to recite step c (“releasing said one or more plasmids from said host cell and onto said matrix or solid medium”), which reflects the language of step b in independent claim 43 and step c in independent claim 45. Applicants respectfully submit that this amended claim language obviates the Examiner’s second point regarding contact between plasmids and the matrix or solid medium of the present invention.

With regard to the first point, the Patent Office seems to be alleging that Applicants must provide additional calculations for one or more additional ratios of plasmid DNA vs. host cell genomic DNA in an effort to somehow support the claim language, but the calculation provided in the First Supplemental Declaration was merely one of several arguments as to why the disclosure of Burgoyne fails to render the present invention obvious to one of ordinary skill in the pertinent art. The calculation on page 6 of the Supplemental Declaration (First Supplemental Declaration) is based on comparing a hypothetical 0.1 microgram sample of total DNA with the 0.1 microgram sample of purified pUC19 plasmid DNA used by Burgoyne (as indicated by the use of the subjunctive tense, the word “if,” and similar indicia in context).

First, Applicants are using the hypothetical calculation to argue against the applicability of Burgoyne, either alone or in combination, with respect to the present invention. Applicants wish to point out that the copy number of the plasmid is irrelevant with respect to Burgoyne, because Burgoyne only discloses binding to a sample of previously purified pUC19 plasmid DNA (i.e., 100% plasmid DNA), rather than isolation of plasmid DNA from a sample of intact cells comprising mixed species of DNA. In a prokaryotic cell (e.g., as in the present invention), the DNA mixture would include both genomic DNA and plasmid DNA. (In a eukaryotic cell, the DNA mixture would be more complex and would include not only genomic DNA and plasmid DNA, but also mitochondrial DNA and, in some cases, chloroplast DNA.) As a result, the disclosure of Burgoyne (isolation of purified plasmid DNA on a card) would not have

rendered the present invention (isolation/purification of plasmid DNA from a DNA mixture in an intact host cell) obvious to one of ordinary skill in the pertinent art.

Second, as noted in the First Supplemental Declaration, an assumption was made concerning the yield of Burgoyne, based on “approximately 100%” of the DNA being detected, according to Burgoyne. In the First Supplemental Declaration, the figure of “99%” was used for purposes of the calculation, but the precise percentage of detected DNA in Burgoyne is not provided – only “approximately 100%.” As a result, based on Dr. King’s calculations, “approximately 1% or 3.4×10^8 molecules of plasmid DNA might not be detected,” according to the calculation in the First Supplemental Declaration – far more than the calculated “ 1.9×10^7 molecules of plasmid DNA which co-purified with the genomic DNA.” Even if the assumption of 99% detection were known to be correct – and no evidence has been produced to allege that it is – a plasmid having even ten times the copy number of pUC19 in the hypothetical mixed DNA sample might still be too low to be detected.

As noted in the Second Supplemental Declaration of Dr. Walter King (filed herewith; “Second Supplemental Declaration”), if one were to use an estimate of 90% DNA detection, resulting in 10% undetected DNA, which would be equal to 3.4×10^9 molecules of undetected plasmid DNA in Burgoyne, for 0.1 μg of 3.4×10^9 plasmid might not be detected and for 0.1 μg of genomic DNA containing plasmids this would be over two orders of magnitude below the detectability of low and even many higher copy abundance plasmids.

Third, as Dr. King discusses in the Second Supplemental Declaration, the above hypothetical calculations presuppose a mixed DNA sample in which two different types of DNA would behave *uniformly* when exposed to the matrix or solid medium of the present invention, rather than a situation in which the ordinarily bulkier, longer genomic DNA might “crowd out” or otherwise tangle the smaller plasmid DNA. As noted in the previously cited excerpts of the Sambrook and Old & Primrose references, these two types of DNA often exhibit different properties. Therefore, if anything the calculations provided in the First Supplemental Declaration are on the conservative side.

Fourth, as Dr. King points out in the Second Supplemental Declaration and as noted above, in a prokaryotic cell (e.g., as in the present invention), the DNA mixture would include both genomic DNA and plasmid DNA. In a eukaryotic cell, the DNA mixture would be more complex and would include not only genomic DNA and plasmid DNA, but also mitochondrial DNA and, in some cases, chloroplast DNA. These other types of non-plasmid DNA could likewise compete with the plasmid DNA of interest and further limit the number of “available sites” on the matrix or solid medium.

Fifth, as mentioned by Dr. King in the Second Supplemental Declaration, the above calculations are based on the purified plasmid DNA sample used in Burgoyne and do not attempt to take into consideration any competing binding by proteins and other macromolecules, which, as noted in the First Supplemental Declaration, would further limit the number of “available sites” on the matrix or solid medium.

Clearly, the present invention provides methods of isolating plasmid DNA from a whole cell of far greater complexity than that of the previously purified pUC19 plasmid sample of Burgoyne.

Therefore, the teachings of Rogers, Burgoyne, and Kahn, either alone or in combination, would not have suggested the present invention to one of ordinary skill in the art with any reasonable expectation of success.

Applicants respectfully draw the Examiner’s attention to the Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, Fed. Reg. 72(195): 57526-57535 (Oct. 10, 2007). The Patent Office has failed to show that the present invention has in any way combined prior art elements according to known methods in these three references to yield predictable results, or that this is a case of simple substitution of one known element for another to obtain predictable results or use or application of a known technique to improve a similar device in the same way. The Patent

Office has not shown that the present invention is the result of predictable variation or that it resulted from the choice from a finite number of identified, predictable solutions having a reasonable expectation of success, nor has it shown that it would have been obvious to try with a reasonable expectation of success. Moreover, there is no teaching, suggestion, or motivation in Rogers & Burgoyne, Burgoyne, and/or Kahn that would have led one of ordinary skill in the art to modify one or more of these references or to combine their teachings to result in the method of plasmid isolation directly from host cells (rather than pre-purified) as in the present invention. [See, e.g., Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, Fed. Reg. 72 (195): 57526-57535, 57529 (Oct. 10, 2007).]

With respect to MPEP 2143, the present invention is not a simple substitution (see, e.g., *In re O'Farrell*, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988)), because there would have been no reasonable expectation of success given the state of the art at the time the invention was made (as discussed above and in previous Amendments) (see also MPEP 2143.02); it is not the result of predictable variation or that it resulted from the choice from a finite number of identified, predictable solutions having a reasonable expectation of success, nor would it have been obvious to try with a reasonable expectation of success (see, e.g., *Pfizer v. Apotex*, 480 F.3d 1348, 82 USPQ2d 1321 (Fed. Cir. 2007); *Ex parte Kubin*, 83 USPQ2d 1410 (Bd. Pat. App. & Int. 2007)), due to the differences in properties between genomic DNA and plasmid DNA; nor was there any teaching, suggestion, or motivation in Rogers & Burgoyne, Burgoyne, and/or Kahn that would have led one of ordinary skill in the art to modify one or more of these references or to combine their teachings to result in the method of plasmid isolation directly from host cells (rather than pre-purified) as in the present invention (MPEP 2143). These points were addressed by the previously filed Declaration of Dr. Walter King, filed March 23, 2009, and the previously filed Supplemental Declaration of Dr. Walter King, filed October 6, 2009, and are also addressed in the Second Supplemental Declaration of Dr. Walter King, filed herewith.

Therefore, it is not intuitive that adding the cells directly would have purified the plasmid DNA, nor would one of ordinary skill in the art have considered it obvious to try with any

reasonable expectation of success given the emphasis in the art of (1) the different properties of genomic DNA vs. plasmid DNA; (2) the need, at least for some purposes, to separate the two; (3) the presence of other nucleic acids (e.g., other types of DNA and RNA) in a whole cell sample; and (4) the presence of proteins and other macromolecules in a whole cell sample.

In view of the foregoing, Applicants respectfully submit that claims 26-27, 33-37, and 39-48 fulfill the requirements of 35 U.S.C. §103(a), and request the Examiner's reconsideration of these claims accordingly.

IV. Additional Remarks

Applicants are anxious to further the prosecution of this important application. If the Examiner has any questions, the Examiner is invited to contact Applicants' undersigned representative (617-517-5516 or 617-239-0100) to schedule a telephone interview regarding the above-referenced important case.

CONCLUSION

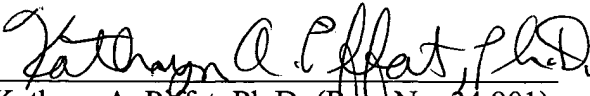
In view of the foregoing amendments and remarks, the present application is respectfully considered in condition for allowance. An early reconsideration and notice of allowance are earnestly solicited.

It is believed that all outstanding rejections have been addressed by this submission and that all the claims are in condition for allowance. If discussion of any amendment or remark made herein would advance this important case to allowance, the Examiner is invited to call the undersigned as soon as convenient.

Applicants hereby request a one-month extension of time for the Amendment and accompanying materials. If, however, a petition for an additional extension of time is required, then the Examiner is requested to treat this as a conditional petition for an additional extension of time and the Commissioner is hereby authorized to charge our deposit account no. 04-1105 for the appropriate fee. Although it is not believed that any additional fee (in addition to the fee concurrently submitted) is required to consider this submission, the Commissioner is hereby authorized to charge our deposit account no. 04-1105 should any fee be deemed necessary.

Respectfully submitted,

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Kathryn A. Piffat, Ph.D. (Reg. No. 34,901)
EDWARDS ANGELL PALMER & DODGE, LLP
P.O. Box 55874
Boston, Massachusetts 02205
Telephone: 617-239-0100
Facsimile: 617-227-4420 (new)

Customer No. 21874